Pompe Disease

Glycogen Storage Disease Type 2

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History

- Described first in 1932 in a 7-month old infant who died of cardiac problems
- Dr. Henri-Gery Hers later connected the condition to glycogen[1] in the muscles and a malfunction of an enzyme later called Acid Alpha-Glucosidase
- Pompe disease became the first in a diverse group of more than 50 currently recognized lysosomal[2] storage disorders
- In 2006, the U.S. Food and Drug Administration (FDA) approved Myozyme as a treatment

[1] Glycogen : short-term fuel reserve in humans

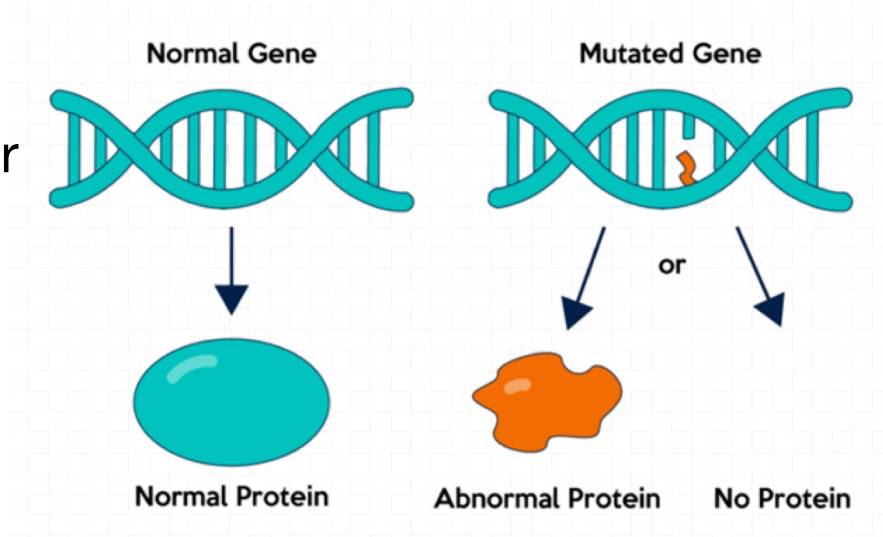
[2] Lysosome : center for cellular clearance and recycling - aids in breakdown of various molecules

Occurrence

- About 1 in every 40,000 births
- Ethnicity differences
  - Incidence as high as 1 in 14,000 in the African-American population
  - Incidence in Caucasians is 1 in 100,000 for early onset and 1 in 60,000 for late onset

Genetics

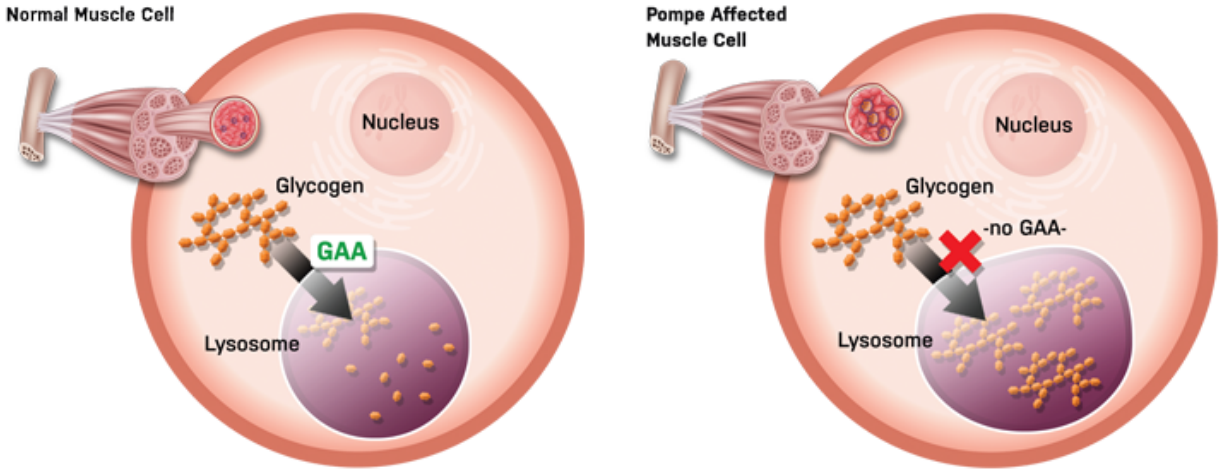
- Over 300 different mutations in the acid alpha-glucosidase (GAA) gene
- These mutations result in either complete or partial deficiency of GAA
  - Complete deficiency: infantile/early onset
  - Partial deficiency: adult/late onset
- Pompe is an autosomal recessive disorder
  - Both parents must be carriers for a child to show symptoms



Digital image retrieved 10/08/2019 from https://kintalk.org/genetics-101/

Biochemical features

- Acid Alpha-Glucosidase (GAA) enzyme deficiency
  - Normal function of GAA : breakdown of glycogen[1]
  - GAA deficiency leads to accumulation of glycogen in the lysosome[2]

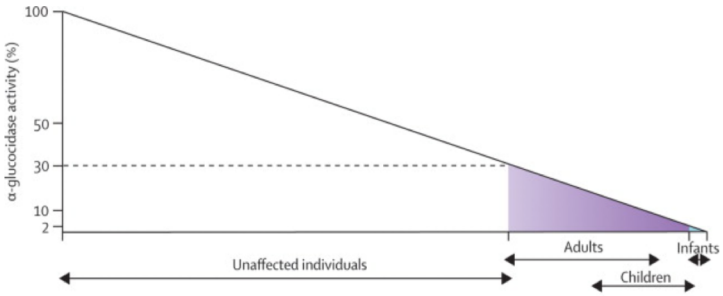


Digital image retrieved 01/30/2020 from

https://www.pompe.com/pc/what-is-pompe/genetics

Symptoms

- Hypertrophic cardiomyopathy - thickened heart muscle limits the heart's ability to pump blood
- Respiratory muscle weakness
- Skeletal muscle weakness - can lead to back pain or issues walking
- Hearing loss - due to cochlear pathology
- Early death if untreated



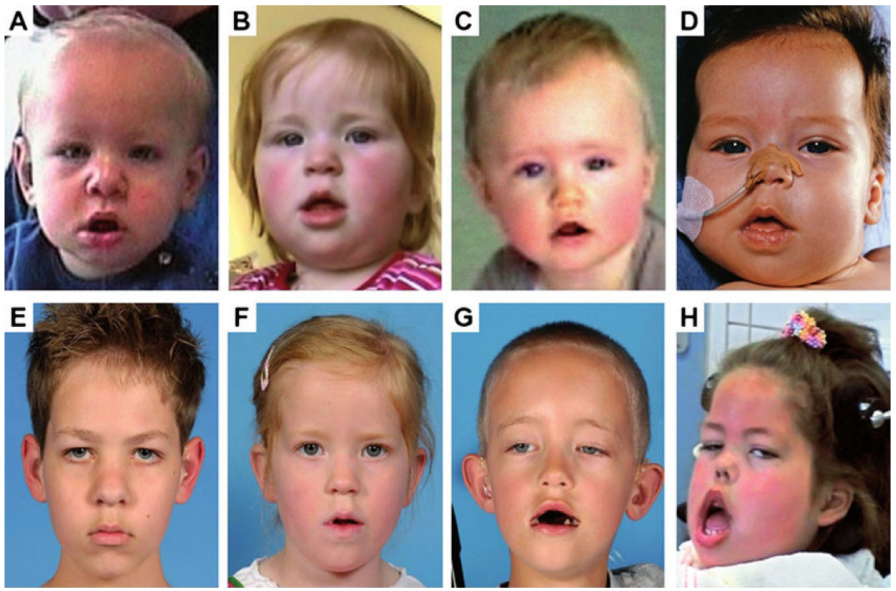
Enzyme activity less than 30% of normal function is considered a deficiency. Age of onset is related to the extent of alpha-glucosidase deficiency. Lower activity leads to earlier onset of disease.

Figure retrieved 11/11/2019 from

A.T. van der Ploeg, A.J. Reuser. (2008) Lancet 372: 1342-1353.

Symptoms that parents will notice

- Hypotonia - inability to support the head
- Missed milestones - sitting, crawling, walking, etc.
- Difficulties swallowing and/or suckling
- Low facial muscle tone
- Diminished deep tendon muscle reflexes
- No response to sound



Progression of facial muscle tone weakness with increasing age in four patients with infantile Pompe disease (top row as they were when first diagnosed, bottom row shows the same patients at an older age while undergoing enzyme replacement therapy).

Figure retrieved 11/11/2019 from

Gelder, Capelle, Carine, Ebbink, et al. (2011). J. Inherit. Metab. Dis. 35, 505-511.

Diagnosis

- Prenatal: enzyme activity assay from embryonic fibroblast sample
  - Skin biopsy in older children: testing of GAA enzyme activity in skin fibroblast cultures. A sensitive, but invasive, test.

- Newborn screening by blood test: measure whether GAA enzyme is active (usually done with a confirmation test)
  - DNA test: a definitive way to rule out other conditions
  - Breathing test: a measure of lung capacity
  - Electromyography: testing electrical activity of muscle tissue
  - Visual heart tests: test for heart abnormalities (e.g., thickening of heart walls, abnormal heartbeat)

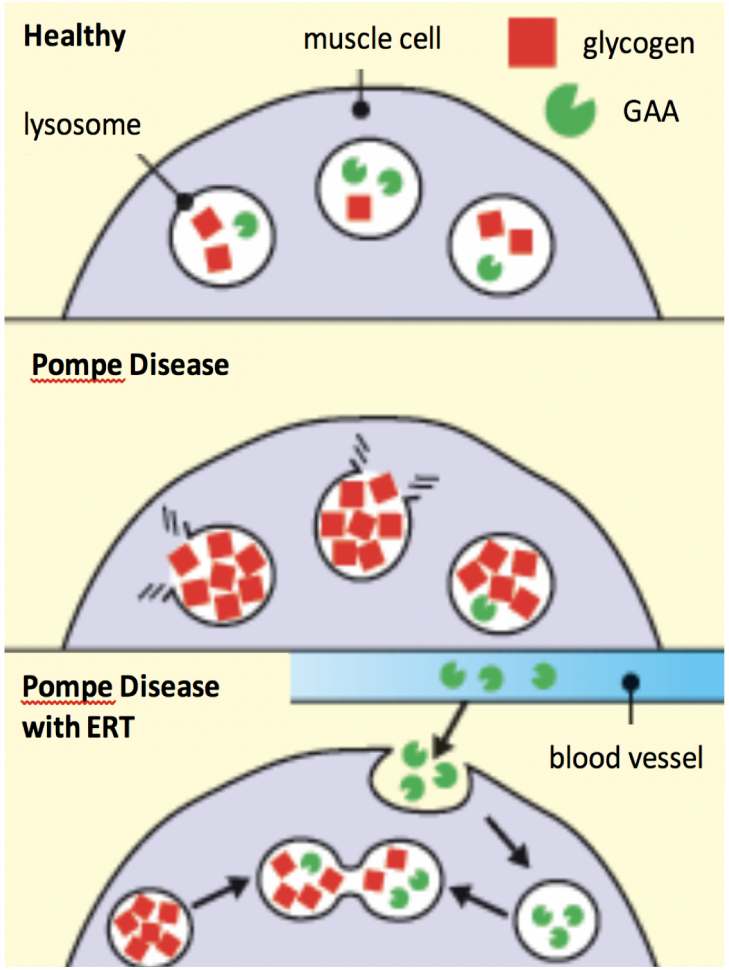
Prognosis

- Major cause of death is heart or lung failure, with median age of death for untreated infants at eight and one-half months
- Later onset of symptoms usually means a better prognosis, with longer survival as well as higher quality of life for a longer period
- With enzyme replacement therapy (ERT), survival and quality of life (independent breathing, walking) improve significantly
- It is still too early to give median age of death for treated infants (this is a success for ERT because a lot of the patients treated are still alive well past usual life expectancy)

Therapy

- Enzyme Replacement Therapy (ERT): an intravenous infusion of α-glucosidase helps maintain normal:
  - Heart size, cardiac function
  - Muscle tone

- Initial treatment is usually 20 mg/kg body weight every 2 weeks.
  - This dose is often increased to 40 mg/kg body weight every 2 weeks, as necessary.



Digital image retrieved and modified 11/15/2019 from http://scriptphd.com/medicine/2010/01/21/review-extraordinary-measures/

Enzyme replacement therapy (ERT)

- ERT medication depends on condition onset/deficiency:
  - Infant/early onset (complete deficiency)
    - Myozyme® - approx. $10,000 USD per prescription
  - Adult/late onset (partial deficiency)
    - Lumizyme® - approx. $20,000 USD per prescription
- Costs for Myosyme and Lumizyme are based on price before insurance or Medicaid reimbursement.
- Immunosuppressive therapy may also be necessary for successful ERT to prevent life-threatening allergic reactions

Images retrieved 10/07/2019 from https://drughut.net/products/myozyme-50-mg-dshp

https://www.lumizyme.com/healthcare/product_support/ordering_lumizyme

Supplementary therapies

- Occupational/physical therapy
  - Minimize muscle weakness and maintain muscle mass
  - Maintain daily motor function for improved quality of life
- Speech therapy
  - Maintain or develop (in young children) speaking ability
- Nutrition therapy
  - Protein-rich diet with appropriate exercise can improve strength
    - Approx. 25-30% protein, 30-35% carbohydrates, and 35-40% fat

Additional support

- The patient or child is not the only one that needs help, the family does as well. The following is a list of support groups that offer more information:
- http://www.lysosomaldiseasenetwork.org/patient-advocacy-support-groups/

★★❖**United Pompe Foundation**
David W. Hamlin
5100 N. Sixth Street, #119
Fresno, CA 93710, USA
Tel. (559) 227-1898, Fax (559) 227-1898
Email: United Pompe Foundation Admin
Website: http://www.unitedpompe.com

❖**Association for Glycogen Storage Disease** (AGSD)
Iris Ferrecchia, President
P.O. Box 896
Durant, IA 52747, USA
Tel. (563) 514-4022
Email: President of the AGSD
Website: http://www.agsdus.org/

Image taken 11/07/2019 of http://www.agsdus.org/

Other initiatives

- Movie: Extraordinary Measures

  - A story of parents with 2 children who diagnosed with Pompe diseases, raised money to help Pompe disease research and clinical trials.

- Pompe Warrior Foundation

  - Started with Go Fund Me page for their son Leo, soon they created foundation to promote research, educate and empower individuals and families affected by Pompe Disease.

Image taken 11/7/2019 of www.pompdiseasefoundation.com

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Pompe disease: Project team

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